

Tractability results for the Double-Cut-and-Join circular median problem

Ahmad Mahmoody-Ghaidary^{1,2}, Cedric Chauve¹, and Ladislav Stacho¹

¹ Department of Mathematics, Simon Fraser University, Burnaby (BC), Canada

² Department of Computer Science, Brown University, Providence (RI), USA

Abstract. The circular median problem in the Double-Cut-and-Join (DCJ) distance asks to find, for three given genomes, a fourth circular genome that minimizes the sum of the mutual distances with the three other ones. This problem has been shown to be NP-complete. We show here that, if the number of vertices of degree 3 in the breakpoint graph of the three input genomes is fixed, then the problem is tractable³.

1 Introduction

Comparative genomics has been an important source of combinatorial and algorithmic questions during the last 20 years, especially the computation of genomic distances and ancestral genomes, as illustrated by the recent book of Fertin *et al.* [3]. Among these problems, the *median* problem is of particular interest: while the distance problem is tractable in many models, the median problem is its simplest natural extension (a distance is a function of two genomes, while the median score is a function of three genomes) and is computationally intractable in most models. Computing median is at the heart of inferring gene order phylogenies and ancestral gene orders [6, 4, 12]. This motivated research on tractability issues of genomic median problems, well summarized in the recent paper [8], as well as on practical algorithms to address it (see [9, 14, 10, 11] and references there).

Roughly speaking, the median problem is as follows: given three genomes G_1 , G_2 and G_3 and a genomic distance model d , find a genome M that minimizes the *cost* of d over G_1, G_2, G_3 defined by $d(M, G_1) + d(M, G_2) + d(M, G_3)$. It is in fact an ancestral genome reconstruction problem, as M can be seen as the last-common ancestor of G_1 and G_2 , with G_3 acting as *outgroup* (i.e. a genome whose last common ancestor with G_1 and G_2 is an ancestor of M). In [8], Tannier *et al.* explored several variants, based on different models of genomes (linear, circular or mixed, see Section 2) and of genomic distances (Breakpoint, Double-Cut-and-Join, Reversals, ...). In particular, they showed that if d is the Double-Cut-and-Join (DCJ) distance, which is currently the most widely used genomic distance, then computing a circular or mixed median is NP-complete. In fact, the only known tractable median problem is the mixed breakpoint median: d is the breakpoint distance and the median can contain both linear and circular chromosomes. From a combinatorial point of view, the central object in the DCJ model is the *breakpoint graph*: the DCJ distance between two genomes with n genes is indeed easily obtained from the number of cycles and paths containing odd number of vertices (odd paths) in this graph [13, 1]. Recent progress in understanding properties of this graph, and especially of the family of *adequat subgraphs*, lead Xu to introduce algorithms to compute DCJ median genomes which are efficient on real data, but do not define well characterized classes of tractable instances [9–12].

In the present work, we show the following result: if the breakpoint graph of three genomes contains a constant number of vertices of degree 3, then computing a DCJ circular median is tractable. To the best of our knowledge, this is the first result defining an explicit non-trivial class of tractable instances related to the DCJ median problem. In Section 2, we define precisely combinatorial representations of genomes, the DCJ distance, breakpoint graphs and the problem we addressed here. In Section 3, we state and prove our main result.

³ Version of November 28, 2011. This paper is currently under peer-review. The results appeared in Ahmad Mahmoody-Ghaidary, *Tractability Results for the Double-Cut and Join Multichromosomal Problem*, MSc thesis, Department of Mathematics, Simon Fraser University, 2011.

2 Preliminaries

Genes, genomes and breakpoint graph Let $A = \{1, 2, \dots, n\}$ represent a set of n genes⁴. Each gene i has a head i_h and a tail i_t . From now, we assume A always contains n genes.

A genome G , with gene set A , is encoded by the order and orientation of its genes along its chromosomes (i.e. its *gene order*), or equivalently by the set of the adjacencies between its gene extremities, that can naturally be represented by a *matching* on the set of vertices $V(G) = \{i_h, i_t | 1 \leq i \leq n\}$ (Fig. 1 (a)). The connected components of the graph whose vertices are $V(G)$ and edges are the disjoint union of the edges of G and the edges $\{i_t, i_h\}$ (forcing gene extremities for a given gene to be contiguous) form the *chromosomes* of G (Fig. 1 (b)). A chromosome is *linear* if it is a path and *circular* if it is a cycle. G is *circular* if it contains only circular chromosomes (perfect matching), *linear* if it contains only linear chromosomes, and *mixed* otherwise. Fig. 1(a,b) illustrates this view of genomes as matchings.

The *breakpoint graph* $B(G_1, \dots, G_m)$ of m genomes G_1, \dots, G_m on A is the disjoint union of these genomes, i.e. the graph with vertex set $V(A)$ and edges given by the matchings defining these m genomes. Following the usual convention, we consider that edges in this graph are colored, with color c_i assigned to genome i ($1 \leq i \leq m$); it results that $B(G_1, \dots, G_m)$ can have multiple edges of different colors (see Fig. 1 (c)).

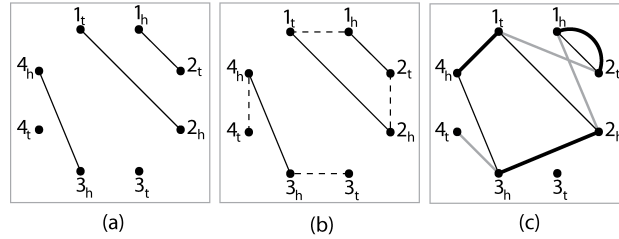


Fig. 1. (a) A genome on 4 genes, with two chromosomes, one circular chromosome with gene order (1 2) and one linear chromosome with gene order (4 - 3), where the sign - indicates a reverse orientation. (b) The same genomes with added dashed edges connecting gene extremities: every connected component of the resulting graph is a chromosome. (c) The breakpoint graph of three genomes (whose edges are respectively light gray, thin black and thick black) on 4 genes.

DCJ distance and median Given two genomes G and M on A , with M being a circular genome, the *DCJ distance* $d_{DCJ}(G, M)$ is given by

$$d_{DCJ}(G, M) = n - c(G, M), \quad (1)$$

where $c(G, M)$ is the number of cycles in $B(G, M)$. So larger $c(G, M)$ implies smaller distance $d_{DCJ}(G, M)$. The general definition of the DCJ distance (when both G and M are mixed genomes) also requires to consider the odd paths⁵ of the breakpoint graph [1], but it is easy to see that the breakpoint graph does not contain odd path if at least one genome is circular. Note that the edges on a cycle in $B(G, M)$ are alternatively from M and G . An (G, M) -*alternating cycle* is an even cycle with edges in M and G alternatively. For simplicity, we may sometimes only call such cycles *alternating cycles*.

A *DCJ circular median* for three genomes G_1 , G_2 , and G_3 , or alternatively for their breakpoint graph $B(G_1, G_2, G_3)$, is a circular genome M which minimizes

$$\sum_{i=1}^3 d_{DCJ}(G_i, M) = 3n - \sum_{i=1}^3 c(G_i, M)$$

⁴ The term *gene* is used here in a generic way, and might include other genomic markers such as synteny/orthology blocks for example.

⁵ An *odd* (resp. *even*) subgraph is a subgraph with an odd (resp. even) number of vertices.

. So a circular genome M which maximizes the the total number of (M, G_i) -alternating cycles (for an $i \in \{1, 2, 3\}$) is a DCJ circular median.

Terminology From now, by *median* we always mean *DCJ circular median*. We denote also by $m(B)$ the sum $d_{DCJ}(G_1, M) + d_{DCJ}(G_2, M) + d_{DCJ}(G_3, M)$ for a median M .

Let $B = B(G_1, G_2, G_3)$ be a breakpoint graph, and let M be a median of B . The graph $B_M(G_1, G_2, G_3) = B \cup M$ (also denoted by B_M when the context is clear) is called the *median graph* of B with the DCJ circular median genome M (using disjoint union). The edges in $G_1 \cup G_2 \cup G_3$ are called *colored edges*, and edges in M are called *median edges*.

A k -cycle in B_M is an (M, G_i) -alternating cycle of length k , for some i , in B_M . We denote the total number of alternating cycles for a median graph M of a breakpoint graph B by $\text{cyc}(B)$ ⁶. If H is a subgraph of B , then $\text{cyc}(H)$ is the maximum number of alternating cycles composed of edges in H , taken over all matchings in H .

A terminal vertex in a graph is a vertex of degree 1. A subgraph of B is said to be *isomorphic to C_k* (resp. P_k) if it is a cycle (resp. path) on k vertices.

Remark 1. The problem we consider in the present work is to compute a DCJ circular median of three given genomes, or equivalently to find a matching in B that maximizes the number of alternating cycles. From this point of view this is a purely graph theoretical problem that can be extended naturally to any edge-colored graph, with the convention that if the graph has an odd number of vertices, then exactly one vertex does not belong to the matching.

Shrinking in a breakpoint graph Shrinking a pair of vertices $\{u, v\}$ or an edge with end vertices u and v was defined in [9]. It consists of three steps: (1) removing all edges between u and v (if there is any), (2) identifying the remaining edges incident to both u and v and with same color, (3) removing u and v . We denote the resulting graph by $B \cdot \{u, v\}$ (Fig. 2).

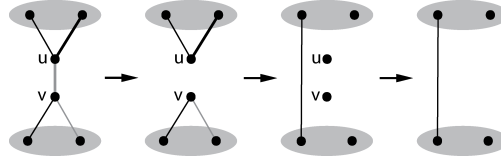


Fig. 2. Illustration of the shrinking of a pair $\{u, v\}$ of vertices of a breakpoint graph.

Proposition 1. Let B be the breakpoint graph of genomes G_1, \dots, G_m , and $u, v \in V(B)$. Suppose that there are k colored edges between u and v . If there exists a median M containing the edge uv , then $\text{cyc}(B) = \text{cyc}(B \cdot \{u, v\}) + k$.

Proof. Consider a median M which contains the edge uv (which implies that both u and v are in the same alternating cycle in B_M). Let $B' = B \cdot \{u, v\}$, $M' = M - \{u, v\}$ (the graph obtained from M by removing u , v and the edge uv).

Let C be an alternating cycle in B_M . If C does not contain u and v , then, obviously, C does not contain any of the k edges between u and v . Thus, C remains unchanged in $B'_{M'}$. Assume now that C contains uv . If the length of C is larger than 2, shrinking $\{u, v\}$ results in a cycle with smaller length in $B'_{M'}$ (the length decreases by 2). Otherwise, if C has length 2, it disappears in $B'_{M'}$. Thus the number of

⁶ Note that $\text{cyc}(B)$ does not depend only on the topology of B , but also on the colors of its edges. Moreover, for different medians M of B , B_M has the same number of alternating cycles, so $\text{cyc}(B)$ does not depend of a particular median.

alternating cycles which disappear in $B' \cup M'$ is k , since there are k edges between u and v . Therefore, $\text{cyc}(B) \leq \text{cyc}(B \cdot \{u, v\}) + k$.

Now suppose N' is a median of B' . By a similar argument, if $N = N' \cup \{u, v\}$, then B_N has $\text{cyc}(B \cdot \{u, v\}) + k$ alternating cycles. So, $\text{cyc}(B) \geq \text{cyc}(B \cdot \{u, v\}) + k$, and, as $\text{cyc}(B) = \text{cyc}(B \cdot \{u, v\}) + k$, we have that M' (resp. N) is a median of B' (resp. B).

3 A class of tractable instances

Our main theoretical result is the definition of a large class of tractable instances for the median problem, namely the ones whose breakpoint graph contains few vertices of degree 3. Obviously, the median problem for three genomes involves a breakpoint graph with maximum degree 3. We show here that the hardness of the problem is due to these vertices of degree 3.

Theorem 1. *Let G_1, G_2 , and G_3 be three genomes. If there exists a median of $B = B(G_1, G_2, G_3)$ with at most ℓ edges whose both end-vertices are of degree 3 in B , then computing such a median can be done in time $O(n^3 \cdot (\ell + 1) \cdot (3^m \cdot m^{2\ell} + 1))$, where m is the number of vertices of degree 3, and n is the number of genes in G_1, G_2, G_3 .*

Remark 2. Note that, as corollaries of this theorem, we have in particular that,

1. if m is bounded, then computing a median is tractable,
2. if ℓ is bounded, then computing a median is Fixed-Parameter Tractable (FPT) (see [7] for a reference on FPT algorithms) with parameter m .

Moreover, if m is not bounded, we can remove some edges incident to vertices of degree 3, so that in the new instance the number of vertices of degree 3 is bounded. Now, by point 1 above, there is a polynomial time algorithm which computes the median of the new instance.

Informally, to prove Theorem 1, we first consider the case where B is a collection of cycles and paths (i.e. has maximum degree 2) and show that a median can be computed in polynomial time. Next, we consider all possibilities (configurations) for matching vertices of degree 3 as median edges. For each configuration, we reduce the breakpoint graph by shrinking and removing some edges to obtain a graph whose connected components are paths or cycles. Having computed all possible configurations for vertices of degree 3 and being able to compute a median for all resulting graphs lead to Theorem 1.

From now, G_1, G_2 , and G_3 are mixed genomes on n genes, and M is a median of these genomes, unless otherwise specified. We denote their breakpoint graph by B , and the median graph by B_M .

3.1 Preliminary results

We first introduce two useful lemmas that give lower bounds on the function cyc in various cases.

Lemma 1. *If B is isomorphic to P_k or C_{2k} , for $k \geq 1$, then for every subgraph $H \subseteq B$, $\text{cyc}(H) \geq \frac{|E(H)|}{2}$.*

Proof. Consider the path $P_k = u_1 u_2 \dots u_k$. Let M be the matching consisting of the edges $u_1 u_2, u_3 u_4, \dots$, and $u_{t-1} u_t$, where $t = 2 \lfloor \frac{k}{2} \rfloor$. Obviously, the number of alternating cycles in $P_k \cup M$ is $\lfloor k/2 \rfloor$, so $\text{cyc}(P_k) \geq \frac{k}{2} \geq \frac{|E(P_k)|}{2}$. Similarly $\text{cyc}(C_{2k}) \geq k = \frac{|E(C_{2k})|}{2}$. See Fig. 3.

Any proper subgraph $H \subset P_k$ or C_{2k} is a union of disjoint paths. If we take the union of matchings described above for each of these paths and call it M , there are at least $|E(H)|/2$ alternating cycles in $H \cup M$. Therefore for any subgraph $H \subseteq B$, $\text{cyc}(H) \geq \frac{|E(H)|}{2}$.

Definition 1. *Let S and T be two subgraphs of B . T is an alternating-subdivision of S if we can obtain an isomorphic copy of T from S as follows: subdivide each edge $e = \{a, b\}$ by an even (possibly zero) number of vertices resulting in a path $av_1 v_2 \dots v_{2k} b$, then remove every second edge, i.e., $v_1 v_2, v_3 v_4, \dots, v_{2k-1} v_{2k}$. We call the removed edges a completing matching for T relative to S .*

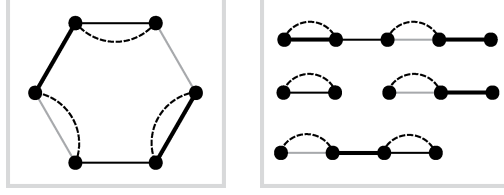


Fig. 3. Median edges (dashed) for cycles and union of disjoint paths.

In the previous definition, note that there might be more than one way to obtain an isomorphic copy of T from S , and consequently, completing matching is not necessarily unique.

Lemma 2. *If T is an alternating-subdivision of S , then $\text{cyc}(T) \geq \text{cyc}(S)$.*

Proof. Let M be a median of S , M' an arbitrary completing matching for T relative to S and $M'' = M \cup M'$. M'' is a perfect matching of T , and each alternating cycle in $S \cup M$ defines a unique alternating cycle in $T \cup M''$ which implies that $\text{cyc}(T) \geq \text{cyc}(S)$ (see Fig. 4).

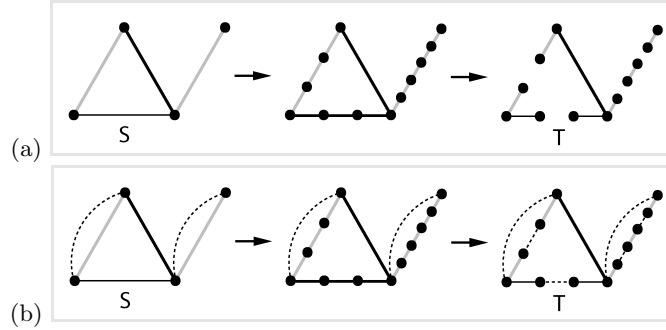


Fig. 4. (a) Obtaining T as an alternating-subdivision of S . (b) Obtaining a matching of T from a median of S (the dashed edges are the median edges and the edges of a completing matching for T relative to S).

3.2 Independence of arbitrary paths and even cycles

In this section we introduce the fundamental notion of *independence* of connected components of cycles and paths in a breakpoint graph.

Definition 2. *Let H be a subgraph of B . An H -crossing edge in a median graph B_M is a median edge which connects a vertex in $V(H)$ to a vertex in $V(B) - V(H)$. An H -crossing cycle is an alternating cycle which contains at least one H -crossing edge. The subgraph H is k -independent if there is a median M for B such that the number of H -crossing edges in B_M is at most k .*

Proposition 2. *Let H be a connected component of B . If H is isomorphic to P_{2k} or C_{2k} , for $k \geq 1$, then H is 0-independent.*

Proof. Let M be a median of B . Suppose M has ℓ H -crossing edges in B_M . If $\ell = 0$, then we are done, so assume that $\ell > 0$. Since H has an even number of vertices, ℓ is even and $\ell \geq 2$. Because H is a connected component in B , each H -crossing cycle contains an even number of H -crossing edges.

Let $C_{M,H}$ be the set of all H -crossing cycles in B_M , and $E_{M,H}^{cr}$ be the set of all H -crossing edges in B_M . Let $X(M)$ be the set of colored edges in all cycles of $C_{M,H}$, and $Y(M)$ be the set of all H -crossing edges in all cycles of $C_{M,H}$.

Case 1. If there is no H -crossing cycle, i.e., $C_{M,H} = X(M) = Y(M) = \emptyset$, we modify M by removing all H -crossing edges, and re-matching the vertices inside of H together and outside of H together. Since ℓ is even, this is always possible and we get a median with no H -crossing edge.

Case 2. From now, we assume that there exists at least one H -crossing cycle. The remainder of the proof relies on a transformation on M that reduces the number of edges in H -crossing cycles, leading to a median with no H -crossing edge.

Step 1. The first step consists of choosing, for each H -crossing cycle, an arbitrary colored edge in H incident to an H -crossing edge from this cycle. Let S be the subgraph of B induced by these chosen colored edges and $T = X(M) - S$.

Claim 1. T is an alternating-subdivision of S . For a vertex $x \in V(S)$ let x_M be the neighbor of x in M . If $u, v \in V(S)$ and $uv \in E(S)$ then, by definition, uv is a colored edge of an H -crossing cycle which is incident to an H -crossing edge. Therefore, there is an alternating path from u_M to v_M , with alternating colored and median edges from that cycle. If this path has t colored edges, we subdivide the edge uv using $2t - 2$ vertices and remove every second edge. Proceeding in this way for every edge $uv \in E(S)$ we obtain an alternating-subdivision T of S .

Claim 2. $\text{cyc}(T) \geq |C_{M,H}|/2$. First, as every colored edge is in at most one alternating cycle and two edges of the same color are not incident to each other, $|E(S)| = |C_{M,H}|$. Also $S \subseteq H$, and by Lemma 1, $\text{cyc}(S) \geq |E(S)|/2$. Finally, from Lemma 2, $\text{cyc}(T) \geq \text{cyc}(S) \geq |E(S)|/2 = |C_{M,H}|/2$.

Step 2. Now we remove all the edges in $E_{M,H}^{cr}$. Let M_S be an arbitrary median of S , M_T the matching for T defined by the union of M_S and an arbitrary completing matching for T respective to S , and $M' = (M - Y(M)) \cup M_S \cup M_T$.

Claim 3. M' is a median of B . First, by removing the edges in $Y(M)$, the total number of alternating cycles decreases by $|C_{M,H}|$. Next, M_S and M_T contain at least $|C_{M,H}|/2$ alternating cycles each (Claim 2 above). Hence, the new matching M' contains at least the same number of alternating cycles than M . By definition of a median, M' can not contain more alternating cycles than M , so it contains the same number of alternating cycles, and is a median of B . Note that this also implies that $\text{cyc}(S) = \text{cyc}(T) = \frac{|C_{M,H}|}{2}$.

Claim 4. $X(M') \subset X(M)$ and $X(M') \neq X(M)$. If there exists $e \in X(M') - X(M)$ then there would be at least one H -crossing cycle induced by M' which is not induced by M_S or M_T , this implies $B_{M'}$ would contain more alternating cycles than B_M , which contradicts the fact that B_M and $B_{M'}$ have the same number of alternating cycles. Next, $X(M') \subset X(M)$, as $E(S) \subset X(M)$ and $E(S) \cap X(M') = \emptyset$ (the vertices in S are matched to themselves). Therefore, $|X(M')| < |X(M)|$.

By iterating the above steps we obtain a median with no crossing cycle. Then, by case 1, we can modify this median to a median without H -crossing edge.

Proposition 3. *Let H be a connected component of B . If H is isomorphic to P_{2k-1} , for $k \geq 1$, then H is 1-independent.*

Proof. We follow the same proof strategy than for Proposition 2. The number of H -crossing edges is odd. If there is no H -crossing cycle, we can remove an even number of them as in case 1 of the proof of Proposition 2, leaving only one H -crossing edge. Otherwise, if we assume that there are H -crossing cycles, we can apply the transformation defined in case 2 of the proof of Proposition 2. It has similar properties, as, from Lemma 1, for every subgraph $H' \subseteq P_{2k-1}$, $\text{cyc}(H') \geq |E(H')|/2$, which implies again that $\text{cyc}(S) = \text{cyc}(T) = \frac{|C_{M,H}|}{2}$.

Proposition 4. *If B contains only cycles and paths, there exists a median of B in which even components have no crossing edge, and each odd path has exactly one crossing edge.*

Proof. This result follows from applying, on an arbitrary median graph, the transformation introduced in the proof of in Proposition 2 to each even/odd path or even cycle of the breakpoint graph, reducing then

the number of crossing edges for each of them, without increasing the number of crossing edges in other components.

3.3 Alternating cycles for arbitrary paths and even cycles

The results of the previous section open the way to computing a median of a breakpoint graph with maximum degree 2 by considering each path or even cycle independently, and matching odd paths into pairs (each defined by a single crossing edge). The main point of the current section is to show that paths and even cycles are easy to consider when computing a median.

Proposition 5. *If $H \subseteq B$ is isomorphic to P_k , for some $k \geq 1$, then $\text{cyc}(H) = \lfloor \frac{k}{2} \rfloor$. Moreover, there exists a median whose edges in H define $\lfloor \frac{k}{2} \rfloor$ alternating 2-cycles, and one crossing edge incident to a terminal vertex of H if k is odd.*

Proof. From Lemma 1, $\text{cyc}(H) \geq \lfloor \frac{k}{2} \rfloor$. We use induction on k to show that $\text{cyc}(H) \leq \lfloor \frac{k}{2} \rfloor$. This obviously holds for $k = 1$. So we assume that $k \geq 2$, and consider a median M for H . If there is no 2-cycle (an alternating cycle consisting of two parallel edges) in H_M , each alternating cycle has length at least 4, and hence at least 2 colored edges. So $\text{cyc}(H) \leq \lfloor \frac{|E(H)|}{2} \rfloor = \lfloor \frac{k-1}{2} \rfloor \leq \lfloor \frac{k}{2} \rfloor$.

Now assume that the median M contains a 2-cycle, with vertices u and v . Shrinking $\{u, v\}$ results in H' that is either a single path with $k-2$ vertices or two paths with p and q vertices such that $p+q = k-2$. In both cases, using induction and the fact that all paths are 0-independent or 1-independent, we can conclude that,

- if H' contains one path, $\text{cyc}(H') \leq \lfloor \frac{k-2}{2} \rfloor + 1 = \lfloor \frac{k}{2} \rfloor$,
- if H' contains two paths, $\text{cyc}(H') \leq \lfloor \frac{p}{2} \rfloor + \lfloor \frac{q}{2} \rfloor + 1 \leq \lfloor \frac{k}{2} \rfloor$.

To obtain a median with exactly $\lfloor \frac{k}{2} \rfloor$ alternating cycles in H , we can simply define median edges by linking successive vertices in H (as in the proof of Lemma 1). If k is odd this forces the unique H -crossing edge (Proposition 3) to contain the last end vertex of H (one of its two end vertices), which has no impact on the number of alternating cycles as, by definition, this crossing edge will not belong to any alternating cycle.

Lemma 3. *If B is isomorphic to C_{2k} , for some $k \geq 1$, then either $\text{cyc}(B) = k$ or $\text{cyc}(B) = k + 1$.*

Proof. Obviously, $\text{cyc}(B) \geq k$. So, we assume that $\text{cyc}(B) > k$. Let M be an arbitrary median of B . Following the proof of Proposition 5, if all alternating cycles in B_M have length at least 4, then the number of alternating cycles is at most k , so there must exist at least one 2-cycle in B_M . Let uv be a colored edge in a 2-cycle: $\text{cyc}(B) = \text{cyc}(B \cdot \{u, v\}) + 1$ (Proposition 1). Moreover $B \cdot \{u, v\}$ is a path, or a cycle, and it is a cycle if and only if the two edges incident to the ends of uv have the same color. If it is a path, Proposition 5 implies that $\text{cyc}(B \cdot \{u, v\}) = k - 1$ and $\text{cyc}(B) = k$, which contradicts the assumption that $\text{cyc}(B) > k$. So $B \cdot \{u, v\}$ is a cycle and the edges incident to uv have same color. By induction on k (note that $\text{cyc}(C_4) = 3$ and $\text{cyc}(C_2) = 2$) we can find a median of $B \cdot \{u, v\}$ with $\text{cyc}(B \cdot \{u, v\}) = k - 1 + 1 = k$ or $\text{cyc}(B \cdot \{u, v\}) = k - 1$, alternating cycles. Hence, $\text{cyc}(B) = k + 1$ or $\text{cyc}(B) = k$.

Some definitions below assume that cycles of B are oriented, so we assume from now that edges of every cycle of B are consistently oriented, clockwise or counterclockwise. Fig. 5 provides an illustration.

Definition 3. *A cycle C_{2k} of B is of the first kind if $\text{cyc}(C_{2k}) = k$, and it is of the second kind if $\text{cyc}(C_{2k}) = k + 1$.*

Definition 4. *Let C be a cycle of B . The signature of a vertex of C is an ordered pair (a, b) such that a and b are the colors of the edges incident to that vertex: a is the color of the incoming edge and b the color of the outgoing edge. Two vertices u and v are diagonal if their signatures are of the form (a, b) and (b, a) .*

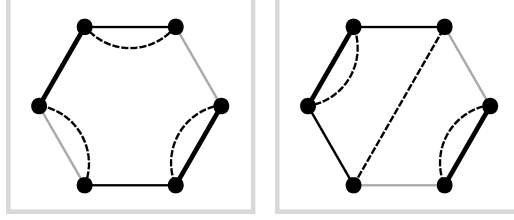


Fig. 5. Dashed edges are median edges: (Left) a cycle C_6 of the first kind — (Right) a cycle C_6 of the second kind; the matched vertices are diagonal

Definition 5. Let M be a median of an even cycle C , and uv and $u'v'$ be edges in M : uv and $u'v'$ cross if u, u', v, v' appear in this order along C . A cross-free diagonal matching for C is a matching whose edges connect pairs of diagonal vertices and no two edges cross.

Lemma 4. Let B be isomorphic to an even cycle of the second kind, and M be a median of B . (1) Each edge in M joins two diagonal vertices, and (2) the edges in M do not cross.

Proof. Let $B = C_{2k}$. We first prove point (1) by contradiction. Assume that $uv \in M$ and that u and v are not diagonal. Let (a, b) and (c, d) be the respective signatures of u and v . Our assumption implies that $(c, d) \neq (b, a)$, and we can distinguish two cases: $(a, b) = (c, d)$ and $(a, b) \neq (c, d)$.

- If $(a, b) = (c, d)$, by shrinking the pair $\{u, v\}$ we obtain a smaller cycle C_{2k-2} , and by Proposition 1, $\text{cyc}(B) = \text{cyc}(C_{2k} \cdot \{u, v\}) = \text{cyc}(C_{2k-2}) \leq \frac{2k-2}{2} + 1 = k$ which is a contradiction, since B is of the second kind. Note that in this case u and v cannot be consecutive vertices on B .
- If $(a, b) \neq (c, d)$, by shrinking the pair $\{u, v\}$, the resulting graph can be either a path with $2k - 2$ vertices, or a cycle and a path, together with $2k - 2$ vertices. In the first case, vertices u and v must be consecutive on B . But now $\text{cyc}(B) = \text{cyc}(C_{2k} \cdot \{u, v\}) + 1 = \text{cyc}(P_{2k-2}) + 1 = \frac{2k-2}{2} + 1 < k + 1$, which is a contradiction, since B is of the second kind. In the second case $\text{cyc}(B) = \text{cyc}(C_{2k} \cdot \{u, v\}) = \text{cyc}(C_\ell) + \text{cyc}(P_m) \leq \frac{\ell}{2} + 1 + \frac{m}{2} \leq \frac{2k-2}{2} + 1 < k + 1$, since paths are either 0- or 1-independent and $\ell + m = 2k - 2$ (note that in the latter case u and v cannot be consecutive). This is again a contradiction, as B is of the second kind.

We now prove point (2). B is of the second kind, as shown in the proof of Lemma 3, there is a 2-cycle containing a colored edge $u'v'$. Moreover, by point (1), vertices u' and v' are diagonal. So $B \cdot \{u', v'\}$ is isomorphic to C_{2k-2} and it must be of the second kind, as otherwise $\text{cyc}(C_{2k}) = \text{cyc}(C_{2k-2}) + 1 = \frac{2k-2}{2} + 1 = k < k + 1$. Obviously, $u'v'$ does not cross with any median edge of M . By shrinking this pair and, by induction on the length of the cycle, applied to $C_{2k} \cdot \{u', v'\}$, the proof is complete.

Lemma 5. Let B be isomorphic to C_{2k} . B is of the second kind if and only if there exists a matching M of B that is cross-free diagonal.

Proof. The necessity follows from Lemma 4. Now assume that there exists a cross-free diagonal matching M on vertices of B . It is easy to see that M contains at least one edge uv where u and v are consecutive on B (note that M is a perfect matching, since B has even number of vertices). If we shrink the pair $\{u, v\}$, the resulting graph is C_{2k-2} and the remaining edges of M are a cross-free diagonal matching for C_{2k-2} . We can complete the proof by induction on k , since $\text{cyc}(C_{2k}) = 1 + \text{cyc}(C_{2k-2}) = 1 + \frac{2k-2}{2} + 1 = k + 1$, and the statement of the lemma is obviously true for $k = 1$ and $k = 2$.

Lemma 6. Let B be isomorphic to C_{2k} . Deciding if B admits a cross-free diagonal matching can be done in time $O(k)$.

Proof. Let $B = v_1 v_2 \dots v_{2k}$. We rely on a simple greedy algorithm, which is in fact a classical algorithm for deciding if a circular parenthesis word is balanced; we present it for the sake of completeness.

The key point was given in the proof of Lemma 5: any cross-free diagonal matching contains at least one pair of consecutive vertices that are matched. Given the circular nature of B , we can extend this property as follows: if u and v are consecutive diagonal vertices and B admits a diagonal cross-free matching, then there exists a matching where u and v are matched. This leads immediately to a greedy algorithm that matches such vertices as soon as they are visited, using a simple stack data structure:

1. Let $M = \emptyset$ be an empty matching.
2. Let S be an empty stack.
3. For $j = 1$ to $2k$
 - (a) if the top element v_i of S is diagonal with v_j , pop it from the stack S and add $\{v_i, v_j\}$ to M .
 - (b) else, push v_j on S .
4. If S is empty, B admits a cross-free diagonal matching, given by M , otherwise it does not admit one.

The time complexity of this algorithm is obviously linear in k .

Proposition 6. *If B is isomorphic to an even cycle of size k ($k \geq 2$), then computing $\text{cyc}(C)$ can be done in time $O(k)$.*

Proof. Immediate consequence of Lemma 3, Lemma 5, and Lemma 6.

3.4 Proof of Theorem 1

We now have all the elements to prove our main result, Theorem 1. We first prove that computing a median of a breakpoint graph of maximum degree two is tractable.

Lemma 7. *If B has maximum degree 2, then there exists a median of B such that every odd connected component of B is connected by median edges to exactly one other odd connected component.*

Proof. Let M be a median as described in the proof of Proposition 4: every even connected component has no crossing edge and each odd path has exactly one crossing edge. Moreover, odd cycles have at least one crossing edge.

Let H be an odd connected component and e one of its crossing edges, connecting H to another odd component H' . Shrinking e results into $(H \cup H') \cdot e$ which is a set of even components and it is then 0-independent. Moreover, as H and H' were distinct connected components of B , from Proposition 1 (with $k = 0$), $\text{cyc}((H \cup H') \cdot e) = \text{cyc}(H \cup H')$.

Repeating this argument for other odd components and the fact that the number of odd components is even (because the number of vertices in the breakpoint graph is even) completes the proof.

Lemma 8. *If B has maximum degree 2 and consists of two odd connected components H_1 and H_2 , of respective sizes k_1 and k_2 , then computing a median of B can be done in time $O(k_1 k_2 (k_1 + k_2))$.*

Proof. For parity reasons, a median M contains at least one edge e between H_1 and H_2 (e is a H_1 -crossing edge). By shrinking e we obtain either one even connected component or two even connected components, and, from Proposition 4, we can compute a median for each connected component independently. This computation requires linear time (Propositions 5 and 6). There are at most $k_1 k_2$ possible candidates for e . Hence computing a median of B is tractable in time $O(k_1 k_2 (k_1 + k_2))$.

Proposition 7. *If B is a breakpoint graph with $2n$ vertices with maximum degree 2, then computing a median of B can be done in $O(n^3)$.*

Proof. We first consider the case where B contains only odd connected components. We define a complete edge-weighted graph K_B as follows:

1. each connected component C defines a vertex v_C ;
2. each edge $\{v_C, v_D\}$ has weight $\text{cyc}(C \cup D)$

By Lemma 8, K_B is computable in polynomial time. We claim it is computable in $O(n^3)$. Suppose B has t components and n_1, \dots, n_t are the number of vertices in each component. So we have $n_1 + \dots + n_t = 2n$. The time to construct K_B is of order

$$\begin{aligned} \sum_{i < j} n_i \cdot n_j \cdot (n_i + n_j) &= \sum_{i < j} n_i^2 \cdot n_j + n_i \cdot n_j^2 \\ &= \frac{1}{3}((2n)^3 - (n_1^3 + \dots + n_t^3)) \leq \frac{8}{3}n^3. \end{aligned}$$

Finally, by Lemma 7 we only need to find a maximum weight matching for K_B , which can be done in $O(n^3)$ by using Edmonds's algorithm [2].

If the breakpoint graph B has maximum degree 2, its connected components are paths or cycles. From Proposition 4 and Proposition 6 we can find the median edges for even components independently. Finally for odd components we find the median edges as described in the first part of the proof.

Proof of Theorem 1. We now assume that B has maximum degree 3.

The main idea is to consider all possibilities for matching the vertices of degree 3 of B . A vertex u of degree 3 can be matched in two ways.

- If it is matched to another vertex of degree 3, by shrinking these two vertices we obtain a smaller graph with fewer vertices of degree 3, and, from Proposition 1, we know precisely the number of alternating cycles (here 2-cycles) lost in the shrinking process, given by the number of genome edges between the two shrunked vertices.
- If it is matched to a vertex of degree less than 3, then one of the edges incident to u is not in any alternating cycle, and we can remove this edge and transform u into a vertex of degree 2 (Fig. 6).

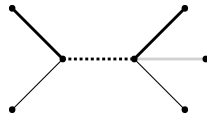


Fig. 6. The dashed edge is a median edge. The gray edge cannot be in any alternating cycle.

Now for each i , $0 \leq i \leq \ell$, we can select $2i$ vertices among all m vertices of degree 3 (there are $O(m^{2i})$ possibilities), compute an arbitrary perfect matching on these $2i$ vertices, and, for each remaining vertex of degree 3, remove an edge incident to this vertex (there are $O(3^{m-2i})$ possibilities). The resulting breakpoint graph B' is of maximum degree 2 and a median can be computed in time $O(n^3)$, whose number of alternating cycles needs only to be augmented by the number of edges between matched vertices of degree 3 in B .

The number of all such configurations is in $O((\ell + 1) \cdot (m^{2\ell} + 1) \cdot 3^m)$ (the term $+1$ is needed to account for the case $m = 0$), which leads to the stated complexity.

4 Conclusion

In this work, we characterized a large class of tractable instances for the DCJ median problem (with circular median and mixed genomes). In fact, we showed that only the vertices of degree 3 make the problem intractable. Also, by removing k edges from the breakpoint graph and decreasing its maximum degree, cost of its median is not bigger than k plus the cost of the main median (i.e. the current cost $-k$ is a lower bound for the cost of the main median). Finally, we showed there is an FPT algorithm for the DCJ median problem, if there exists a median such that the number of its edges connecting two vertices of degree 3 is bounded.

Our work also shows that the multiplicity of solutions (i.e. medians) is likely to happen when dealing with breakpoint graphs with long paths or even cycles, as we showed that such components can admit several optimal medians. Hence, our results, as they stand now, are of interest more for computing the score of a median than for computing actual medians that can be seen as realistic ancestral genomes. However, the problem of uniform sampling of optimal median is worth being explored, even in the simpler setting of breakpoint graphs of maximum degree 2 in a first time.

From a theoretical point of view, our work raises several questions. First, it leaves open the possibility that the DCJ median problem is FPT. Using the number of vertices of degree 3 as a parameter is a natural approach, although this seems to be a difficult question to address. The next obvious problem is to extend our approach to the case of a mixed or linear median. This would require to better understand the combinatorics of odd paths in the breakpoint graphs in relation to medians. The simpler problem to find an optimal way to remove exactly one edge from each circular chromosome of a circular median while minimizing the number of destroyed alternating cycles is also open. Extending our results to the related *DCJ halving problem* [8] is also a natural question.

Another interesting question is about expanding the breakpoint distance toward the DCJ distance: for two genomes G_1 and G_2 on n genes, their breakpoint distance is equal to

$$d_{BP}(G_1, G_2) = n - a(G_1, G_2) - \frac{1}{2}e(G_1, G_2).$$

The parameters $a(G_1, G_2)$ and $e(G_1, G_2)$ are also equal the number of 2-cycles and 1-paths (P_1) in the breakpoint graph $B(G_1, G_2)$, respectively. The DCJ distance of these genomes is:

$$d_{DCJ}(G_1, G_2) = n - c(G_1, G_2) - \frac{p(G_1, G_2)}{2},$$

where $c(G_1, G_2)$ and $p(G_1, G_2)$ are the number of (even) cycles and odd paths in the $B(G_1, G_2)$, respectively. This motivates us to define a dissimilarity function as follows:

$$d_{(i,j)}(G_1, G_2) = n - c_i(G_1, G_2) - \frac{1}{2}p_j(G_1, G_2),$$

where $c_i(G_1, G_2)$ is the number of (even) cycles with at most $2i$ vertices, and $p_j(G_1, G_2)$ is the number of odd paths with at most $2j - 1$ vertices. By considering this dissimilarity measure, the median problem is tractable when $i = j = 1$, since $d_{(1,1)} = d_{BP}$. By taking $i = j = \infty$ we have $d_{(\infty,\infty)} = d_{DCJ}$, and the median problem would be intractable. A natural question is then to understand for which values of i and/or j the median problem is tractable, or FPT.

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